

SHORT REPORT

Vascular Manifestations of Type IV Ehlers–Danlos Syndrome

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Ehlers–Danlos syndrome (EDS) is a hereditary disorder of the connective tissue. Ten different types of EDS have been described, most of which are associated with skin hyperflexibility and joint hypermobility. The type most frequently encountered by surgeons is the arterial ecchymotic type, or type IV. The phenotypical variance that characterizes EDS can make recognition difficult. The diagnosis is often made after vascular or gastrointestinal complications have occurred. We are describing a young pregnant patient with EDS type IV who developed a carotico-cavernous fistula, a crural artery pseudoaneurysm and died due to spontaneous intestinal rupture.

Keywords: Carotico-cavernous fistula; Ehlers–Danlos syndrome; Pseudoaneurysm.

Introduction

Ehlers–Danlos syndrome (EDS) is a hereditary disorder of the connective tissue. Ten different types of EDS have been described, most of which are associated with skin hyperflexibility and joint hypermobility. The phenotypical variance that characterizes this syndrome often makes recognition difficult, and failure to recognise the disease is not uncommon. The diagnosis is often not made until catastrophic vascular or gastrointestinal complications occur.

The type most frequently encountered by surgeons is the arterial ecchymotic type, or type IV. It is a rare form of EDS with a prevalence of less than 1 per 100,000.¹ We are describing a young pregnant patient with EDS type IV who developed a carotico-cavernous fistula, a crural artery pseudoaneurysm and died due to spontaneous intestinal rupture.

Case Report

A 30-year-old female (previous six uneventful pregnancies) during her first trimester of pregnancy noticed a pulsing noise in her head, right eye proptosis, increased lacrimation and a mild reduction in right ocular abduction. A clinical diagnosis of a spontaneous carotico-cavernous fistula (CCF) was confirmed on MRI. She was kept under monthly surveillance due to the early stage of her pregnancy, and the need to avoid prolonged radiation exposure at any endovascular procedure. An intervention was carried out at 28 weeks of pregnancy due to an increase in intra-ocular pressure, reduced right acuity and a worsening of the abduction defect. The fistula was closed with endovascular technique using balloon through the femoral artery without any immediate complications (Fig. 1). Three days later, she developed a right cavernous sinus thrombosis. She was treated conservatively accompanied by a 2-week course of low dose steroid. To avoid opening up the CCF, anticoagulation was avoided. An elective caesarean section was planned at 38 weeks.

Two weeks later, she presented as an emergency, with sudden onset pain and bruising in the right calf. There was no history of trauma. A duplex scan

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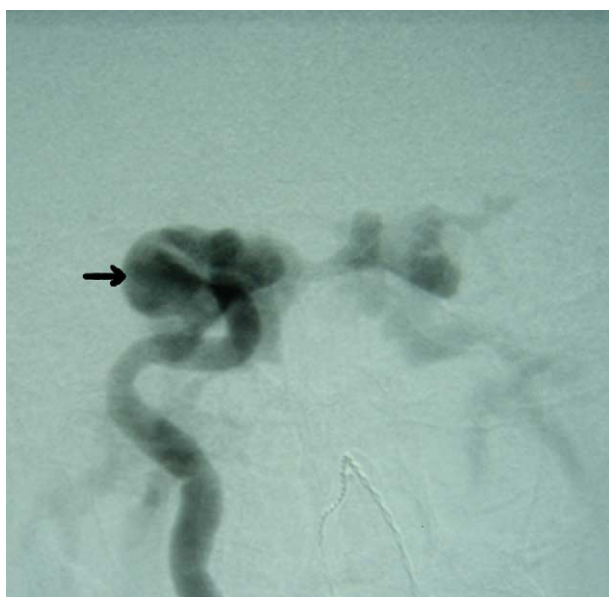


Fig. 1. Cerebral angiography showing a right carotico-cavernous fistula (arrow).

requested to rule out deep venous thrombosis, demonstrated a posterior tibial vein thrombosis and a pseudoaneurysm ($5 \times 3 \text{ cm}^2$) arising from a posterior



Fig. 2. Duplex scan showing a pseudoaneurysm of the right posterior tibial artery.

tibial artery (Fig. 2). Seventy percent of the aneurysm was thrombosed and was compressing the posterior tibial vein. A large haematoma in the right groin from angiography 6 weeks previously was noted, as was one in her right calf. At that point, she revealed a history of easy bruising from childhood. Her skin was also noted to be thin, though the remainder of the systemic examination was normal.

On this basis a provisional diagnosis of a collagen vascular disease e.g. Ehlers–Danlos syndrome, was made. MRI of the thorax and abdomen were normal as was arterial duplex scan of the upper extremities and left lower limb. Two days later she had sudden onset severe pain in the abdomen requiring laparotomy, which revealed spontaneous jejunal multiple perforations. The bowel loops were thin as was the mesentery. After bowel resection end-to-end anastomosis was performed. The baby was delivered prematurely at same time by caesarean section and was taken to paediatric intensive care unit. The postoperative period was complicated by severe infection and both mother and baby ultimately died because of sepsis. Bowel was sent for histology (Fig. 3).

Histology

Macroscopically the bowel wall appeared thinned and there was evidence of perforation. Microscopically the mucosa and submucosa were either normal or showed minor changes including oedema and congestion. There were no ischaemic changes in any of the bowel resections. The major abnormality was in the muscularis propria in form of focal and segmental loss of both longitudinal and circular smooth muscle coats with patchy replacement of the smooth muscle by fibrous tissue. The pathological features described are those of a visceral myopathy and are consistent with EDS although similar findings can be found in visceral myopathies associated with other connective tissue disorders (e.g. systemic sclerosis).

Discussion

In 1899, Edward Ehlers reported a patient with group of symptoms including recurrent haematomas, lax digits, and extensible skin. Nine years later, Henri-Alexandre Danlos described a triad of similar symptoms.² In 1967 Andras Barbaras described type IV EDS (vascular Ehlers–Danlos syndrome).³ It is a heterogeneous genetic disorder and it is, therefore, not surprising that patients present with various clinical scenarios. Type IV is the most malignant form of EDS

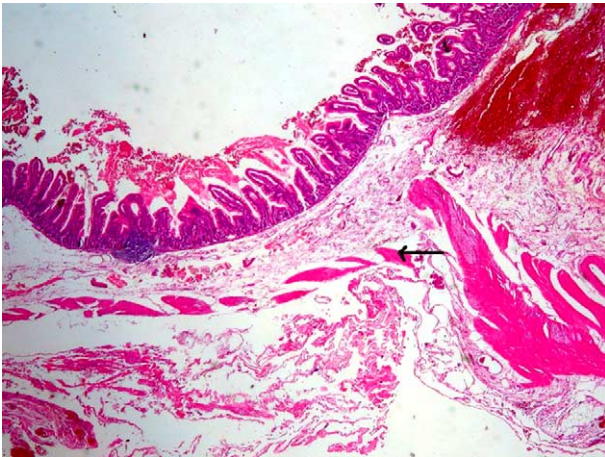


Fig. 3. Histopathology of the small bowel (H&E staining, $\times 40$) demonstrates segmental loss of smooth muscles of the muscularis propria (arrow).

because of the high likelihood of developing spontaneous blood vessel rupture from aneurysms, dissections, transmural tears and rupture of the uterus and bowel. Full expression of the syndrome is rare, and incomplete manifestations are common.

There are five types of collagen in humans distinguished by the composition of their three subunits. Type III collagen is found in highly vascular structures such as blood vessels and liver. Type IV EDS causes a defect in the pro- α -1 III collagen chain resulting from mutations in the COL3A1 gene. It results in reduced or abnormal secretion of type III collagen and, thus, spontaneous visceral and vascular ruptures, and complications of surgical and radiological interventions.

In childhood, many individuals with vascular EDS are thought to have coagulation disorders. In adulthood, four main clinical findings, including facial structural abnormalities, easy bruising, translucent skin with visible veins and rupture of vessels, gravid uterus or intestines contribute to the diagnosis. The literature points out that only 16% of the patients had symptoms suggesting EDS before a vascular event occurred.⁴ Easy bruising appeared to be the most consistent clinical feature, occurring in 66% of patients. Hyperextensibility of the joints are present in 60% and thin or semitransparent skin is seen in 33% of individuals.² Our patient, in retrospect had a history of easy bruising, transparent skin, rupture vessel and hollow viscera and carotid cavernous fistula, without additional joint manifestations.

The diagnosis of EDS type IV is made on clinical findings and confirmed by culture of dermal fibroblasts for type III procollagen molecules. Genetic testing can identify a mutation in the COL3A1 gene

coding for type III procollagen.^{2,5,6} Special attention must be taken when evaluating these patients. Arteriography in EDS is associated with 67% complication rate and a 17% mortality rate.⁴ Therefore, to evaluate vascular system non-invasive imaging such as CT, MRI or Duplex scan should be used.

There is no current medical treatment for EDS, and all surgical procedures should be conservative. Rupture of a vessel in a closed space may wall off because of tamponade, however, in such cases; surgical intervention may be deleterious. Ligation of the vascular rupture has been shown to be the most successful operation. If arterial bypass is required precautions such as use of tourniquets or balloon for vascular occlusion, interrupted anastomosis and use of cuff or pledgets to buttress the suture should be taken into consideration. Endovascular stents should be used with caution as complications can arise easily at access and stent site. Whether there is a role for the repair of the unruptured aneurysm in these patients is not clear.²

Carotid cavernous fistula (CCF) is the most frequent neurovascular complication of EDS type IV. These are abnormal communications between the intracavernous carotid artery and the venous plexus of the cavernous sinus. The spontaneous variety develops in patients with intracavernous aneurysms or in individuals with vascular wall fragility especially in vascular EDS. There is no consensus on the best endovascular approach to closure of this fistula in patients with type IV EDS due to rarity of the disease and use of different approaches. If the diagnosis is known then advantage of using transvenous route for closure of fistulae can be used, as iatrogenic injury to a low pressure vein can be less deleterious than an arterial injury. Use of coils may be superior to a balloon as they are softer, easier to control, smaller delivery devices, less pressure on the sinus and are exchangeable.¹ Number of authors has described neurovascular complications of EDS. Debrun *et al.* and Graf reported three and two cases of spontaneous CCF. Halbach *et al.* reported on four patients with EDS type IV in their series of 212 patients with direct CCF.⁷

Brees described a similar case to this in 1995, where a 29-week pregnant woman presented with external iliac artery rupture. Further jejunal rupture and aortic disruption lead to her demise.⁸ These cases signify the importance of acute abdomen in these patients. Pepin⁶ in a series of 220 patients with type IV EDS showed bowel rupture and sepsis to be responsible for death in 8% of patients. They showed that gastrointestinal rupture tends to occur earlier in age than the vascular rupture. Only 136 patients survived a first complication. Out of 136 only 52 had a second recorded

complication, which was fatal in six patients. Overall, only 21% of the patient had more than one complication. Perforation of the small bowel, was uncommon and sigmoid colon was the main site of perforation.

The prognosis of EDS type IV is poor and most patients' die before the age of 40 years. Survival beyond 50 years is rare. The arterial complications are the cause of death in majority of the patients. The average age at the time of the first vascular or visceral complication is 24 years, with 12% mortality. The risk of major complication by age 40 is 80%. The mortality associated with vascular rupture can be as high as 45%, compared with the hollow viscus rupture mortality of 20%.⁹

Vascular EDS has an autosomal dominant inheritance pattern, individuals and families must be informed of the 50% risk of transmission to the offspring of affected individuals. In addition, women with type IV EDS have a 25% risk of death with each pregnancy.⁹ Although several pregnant women died of uterine rupture at term, it is still not known whether the use of elective caesarean section would decrease mortality. It is important to be aware of the diagnosis prior to pregnancy to have high index of suspicion for arterial or viscus perforation in the face of acute findings.

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